

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
14 February 2002 (14.02.2002)

PCT

(10) International Publication Number
WO 02/11737 A2

(51) International Patent Classification⁷: **A61K 31/7076**,
A61P 29/00

(21) International Application Number: PCT/EP01/08643

(22) International Filing Date: 26 July 2001 (26.07.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
MI2000A001827 4 August 2000 (04.08.2000) IT

(71) Applicant (*for all designated States except US*): **UNIVERSITA' DEGLI STUDI DI MILANO** [IT/IT]; Via Festa del Perdono, 7, I-20122 Milano (IT).

(72) Inventor; and

(75) Inventor/Applicant (*for US only*): **FERRERO, Maria, Elena** [IT/IT]; Via Festa del Perdono, 7, I-20122 Milano (IT).

(74) Agents: **MINOJA, Fabrizio** et al.; Bianchetti Bracco Minoja S.r.l., Via Rossini, 8, I-20122 Milano (IT).

(81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

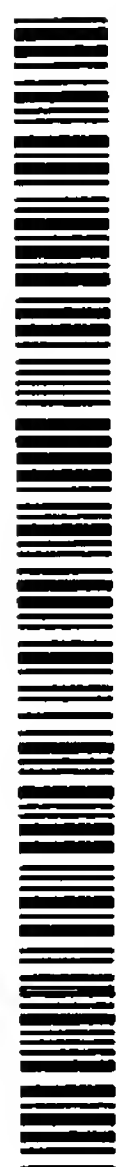
Published:

— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: **ANTI-INFLAMMATORY MEDICAMENT**

(57) Abstract: The use of adenosine-5'-triphosphate-2',3'-dialdehyde (oATP) as a medicament useful for the treatment of inflammatory conditions is disclosed.



WO 02/11737 A2

ANTI-INFLAMMATORY MEDICAMENT

The present invention relates to the use of adenosine-5'-triphosphate-2',3'-dialdehyde (oATP) in the preparation of medicaments useful for the treatment of inflammatory conditions.

5 The oATP molecule derives from ATP by oxidation of the hydroxyls present at the ribose 2'- and 3' positions to dialdehydes. Such an oxidation can be carried out with a periodic acid salt, as described in P. N. Lowe et al., "Preparation and chemical properties of periodate-oxidized adenosine triphosphate and some related compounds", Biochemical Society Transactions, Vol. 7:1131-1133, 1979.

10 ATP 2',3'-dialdehyde derivative is traditionally used as affinity marker for enzymatic nucleotidic sites (Easterbrook-Smith, B., Wallace, J.C. & Keech, D.B. (1976) Eur. J. Biochem. 62, 125-130), because it is capable of reacting with the lysine unprotonated residues present in the nucleotidic sites to form Schiff bases or dihydromorpholino derivatives (Colman, R.F. (1990) in The
15 Enzymes – Sigman, D. S., and Boyer, P.D., eds – Vol 19, pp. 283-323, Academic Press, San Diego). The oATP molecule has also been used to study platelet activation and inhibit stimulation of chicken skeletal muscle by ATP (Pearce, P.H., Wright, J.M. Egan. C.M. & Scrutton, M.C. (1978) Eur. J. Biochem. 88, 543-554; Thomas, S.A., Zawisa, M. J., Lin, X. & Hume, R.I.
20 (1991) Br. J. Pharmacol. 103, 1963-1969). Furthermore, studies on macrophage cell lines proved that oATP is able to block the plasmatic membrane permeabilisation effect induced by ATP, to reduce the hydrolysis level of exogenous ATP by membrane ecto-ATPases and to inhibit the swelling, vacuolisation and cellular lysis effects induced by ATP (Murgia et al. The
25 Journal of Biological Chemistry, (1993) by The American Society for Biochemistry and Molecular Biology, inc., Vol. 268, No. 11, pp 8199). oATP

has been suggested to have antagonistic activity on P2z/P2X7 purinoceptors. IL-1 β (interleukin 1 β) LPS (= lypopolysaccharide) – dependant release from microglial cells expressing P2z/P2X7 is in fact selectively inhibited by oATP (Ferrari D. et al., J. Exp. Med., (1997) Vol. 185, N. 3, Pag. 579-582).

5 It has now been found that oATP exerts *in vivo* remarkable anti-inflammatory and antinociceptive effects. As experimental model, a unilateral inflammation in rat hind paw, after intraplantar injection of Freund's complete adjuvant (FCA), has been used. The controlateral paw of treated animals, as well as that of untreated animals, were used as controls. Inflammation induced
10 by FCA was evidenced, from 3 h until 24-48 h following injection, by increase in paw volume, hyperthermia and hyperalgesia. The latter was evaluated by an algesyometric test (paw pressure test) capable of evaluating the nociceptive threshold. Intraplantar injection of oATP significantly reduced pain sensing (nociception), i.e. it increased nociceptive threshold. Different doses of oATP
15 always induced a significant, dose-dependent analgesic effect, lasting approximately 12-24 hours, with an effect peak already one hour after the administration. Furthermore, paws of oATP-treated rats showed reduction of the other inflammatory signs (swelling and hyperthermia). In a further test, comparison between oATP and diclofenac, a known anti-inflammatory drug
20 used in arthritic pathologies, proved that oATP induces a significantly higher analgesic effect than diclofenac. A test in which rats were pre-treated with fucoidin, a leukocyte diapedesis inhibitor, showed that oATP activity is independent of leukocyte recruitment at the inflammation site. ATP levels at the inflammation sites were significantly higher in untreated animals, which
25 suggests that oATP may somewhat block exogenous ATP production, thus preventing its pro-inflammatory activity.

The present invention relates to the use of oATP as medicament for the treatment of inflammatory and pain conditions. The invention further relates to

pharmaceutical compositions containing oATP as active ingredient, together with pharmaceutically acceptable excipients. Suitable forms for the oral, topical or parenteral administrations are, for example, tablets, sugar coated pills, capsules, granulates, powders, suppositories, syrups, solutions, suspensions, creams, ointments, gels, pastes, lotions, emulsions, spray. The pharmaceutical compositions can be prepared according to what described in Remington's Pharmaceutical Sciences Handbook, Mack Pub. Co., NY, USA, XVII Ed. The amount of active ingredient per unitary dosage may range from 0.05 to 100 mg per Kg body weight, to be administered once or more times daily, depending on the severity of the disease to be treated and the conditions of the patient. The daily dosage will usually range from 1 to 300 mg, preferably from 10 to 100 mg.

The compound of the invention may also be used in combination with other currently used anti-inflammatory drugs.

The following example further illustrates the invention.

Example 1: oATP pharmacological activity

Induction of inflammation in rats

Male Fischer inbred rats (Charles River Italy, Calco, Lecco, Italy) weighing about 250 g were used. Rats, under brief isoflurane anaesthesia received an intraplantar injection of Freund's complete adjuvant (FCA) (0.15 ml) into the right hind paw. This injection induced a unilateral inflammation (from 3 h until 24-48 h following injection) evidenced by increase in paw volume, hyperthermia and hyperalgesia. Hyperalgesia was assessed by an algesyometric test, using an analgesyometer (Ugo Basile, Comerio, Italy) to determine the paw pressure threshold, expressed in grams, namely the pressure required to elicit paw withdrawal, which indicates the nociceptive threshold value. 6 to 8 rats were used for each test. During these trials, animals were treated according to the "standard ethical guidelines" (NIH, 1985).

Treatment with oATP

Rat inflamed paw received, 24 hrs after FCA injection, intraplantar injection of different doses of oATP (56 to 336 μ M), considering time 0 the moment of oATP injection. The nociceptive threshold values obtained are reported in the following Table 1.

TABLE 1

NOCICEPTIVE THRESHOLD OR "PAW PRESSURE THRESHOLD"

	OATP 56 μ M	112 μ M	224 μ M	336 μ M
0'	60 \pm 1.6	65 \pm 2.0	50 \pm 1.5	60 \pm 1.9
10 30'	120 \pm 2.1*	140 \pm 3.5*	350 \pm 5.4*	300 \pm 3.4*
60'	190 \pm 2.3*	180 \pm 4.2*	400 \pm 10.3*	=> 750 *1
90'	85 \pm 2.5*	150 \pm 3.8*	300 \pm 11.2*	=> 750 *2
120'	75 \pm 1.8*	100 \pm 3.0*	185 \pm 7.1*	600 \pm 20.8*
240'	75 \pm 2.6*	105 \pm 4.3*	180 \pm 8.9*	550 \pm 18.4*

*1.2 = cut off

Data are expressed as mean \pm S.E.M. of paw pressure threshold (evaluated in g) $p < 0.05$ vs. time 0' (untreated inflamed paw)

* Mann-Whitney test.

Similar results were obtained using oATP 35 μ m in place of oATP 56 μ m or inducing the inflammatory process (FCA injection) for 6 or 12 h instead of 24 h. Furthermore, oATP treated paws were less painful and also showed reduction of inflammatory signs (swelling, hyperthermia) compared with untreated paws.

A dose-dependent effect of oATP was evidenced, although already significantly high effects were attained at the minimal dose used. Lower doses had however a less lasting analgesic effect in time, possibly due to incomplete saturation of P2X7 receptors.

The effect of the maximal oATP dose used was tested in a further set of experiments, for more prolonged times, on rat paws in which the inflammatory

process had been induced 48 hrs before (table 2). The data prove that oATP injection significantly increases nociceptive threshold values for an exceedingly long time, although progressively decreasing in time.

TABLE 2

5	<u>NOCICEPTIVE THRESHOLD OR "PAW PRESSURE THRESHOLD"</u>	
		OATP336 μ M.
	0'	55 \pm 2.0
	30'	210 \pm 10.7
	60'	360 \pm 25.8
10	90'	395 \pm 30.2
	120'	450 \pm 38.1
	180'	550 \pm 45.9
	240'	690 \pm 56.6
	12 hours	400 \pm 29.7
15	24 hours	210 \pm 7.2
	26 hours	190 \pm 3.3

The nociceptive threshold values of the control paws (both noninflamed controlateral and untreated paws) were approximately 100-150, expressed as nociceptive threshold or paw pressure threshold and evaluated in g.

20 Intraplantar injection of ATP (0.9 mmoles) (extracellular ATP is cytolytic and therefore possibly able to initiate a nociceptive signal) induced reduction of nociceptive threshold significantly higher in noninflamed paws than in inflamed paws (values of 120 \pm 3.2 to 25 \pm 3.0 found in noninflamed paws, 240' after intraplantar injection of ATP) in comparison with a decrease
 25 from 65 \pm 4.2 to 50 \pm 4.1 in inflamed paws. This result possibly indicates that cytolytic ATP is already present in higher amounts in inflamed paws than in noninflamed ones. On the other hand, oATP was effective in increasing nociceptive threshold, for a short time, also in noninflamed paws, being already
 30 effective at the lowest oATP concentration (=56 μ M). Dose/effect curves in noninflamed paws were in fact superimposable (until 120' after oATP administration) using different concentrations of the molecule. In order to

ascertain whether oATP analgesic effect was somewhat related to the activation of inflammatory cells able to produce endogenous β -endorphins, some rats were intravenously injected with fucoidin (10 mg/kg). Fucoidin in fact inhibits leukocyte diapedesis and their accumulation at the inflammation site. Pre-treatment with fucoidin was carried out in both paws, 30' before FCA injection in one of the rat paws. Pain pressure threshold (PPT) was measured in both noninflamed and inflamed paws, before and after oATP injection (224 μ m). The obtained results are reported in the graphics of Figure 1. oATP injection did not significantly change PPT values in noninflamed paws, while in inflamed paws oATP treatment restored PPT levels which had been severely reduced by the injection of pro-inflammatory FCA. oATP analgesic effect was therefore independent of leukocyte recruitment.

Finally, oATP antinociceptive efficacy was compared with that of a known anti-inflammatory and analgesic drug, diclofenac. After evaluation of the basal pain threshold, unilateral inflammation of the hind paw of rats was induced by FCA injection. 3 Hours after the injection, animals were divided in 2 groups, which were treated locally one with oATP (336 μ M) and the other with diclofenac (15 mg). oATP analgesic efficacy was significantly higher than that of diclofenac (results of a typical trial are reported in Figure 2). oATP and diclofenac concentrations were selected as to allow good dissolution of the molecule in sterile saline, before the intraplantar injection in rats.

Finally, intravenous injection of oATP in rats, at the tested intraplantar doses, induced dose-dependent pain relief for approximately two hours, although reflex were apparently still present.

ATP content was assessed in oATP treated rat paws and controlateral untreated ones. Paw subcutaneous tissues were removed from both inflamed and noninflamed paws and rapidly frozen in liquid nitrogen. The frozen tissue samples were weighed, homogenised in phosphate buffer, then treated with

K₂CO₃ and neutralised, finally centrifuged. The supernatant was used for ATP assay, following the luminescence method.

ATP values were significantly higher in homogenates from untreated paws than in oATP treated paws (1050±90 nmoles/g fresh tissue in untreated animals, vs. 320±22 nmoles/g fresh tissue in oATP treated animals – each value is the mean ± S.E.M. of 7 experiments). This indicates that oATP blocks the production of exogenous ATP by some tissular structure, binding to its membrane receptors, thereby reducing the damage induced by exogenous ATP.

Example 2: modification of ATP content in peripheral subcutaneous tissues following oATP treatment.

- Assay of ATP content in rat paw.

We determined in a separate group of rats the modifications in ATP content induced in the plantar tissue by the inflammatory process and/or by oATP treatment. At established times, paw subcutaneous tissues were removed and rapidly frozen in liquid nitrogen, with the aim of blocking any metabolic activity. The frozen tissue was homogenized with a polytron (Kinematica GmbH, Luzern, Switzerland) in ice-cold 6% (w/v) HClO₄ to extract nucleotides. The homogenate was centrifuged and the supernatant was used for ATP determination, following the procedure previously described (Marni et al., Transplantation (1988), 46: 830-835). ATP assay was performed by luminescence method (Ferrero et al., Res Commun Chem Path Pharmac 1984; 45: 55-67).

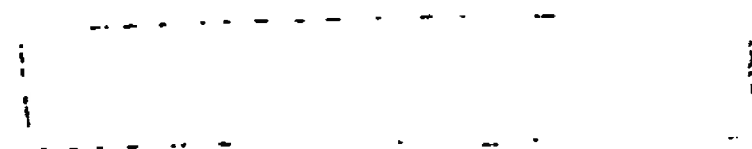
- Results

We measured ATP levels, in inflamed (by 24 h FCA treatment) and noninflamed paws treated with oATP, at 6 and 12 h following oATP administration, and in controlateral untreated paws. As reported in figure 3, in noninflamed tissues oATP treatment did not significantly change ATP levels: the data could express the intracellular levels of the metabolite, which is not

significantly modified by oATP treatment. On the contrary, the levels of ATP in inflamed tissues, significantly higher than in non inflamed tissues, were significantly reduced by oATP treatment. In fact the release of ATP (extracellular ATP) from cells requires their damage and occurs during inflammatory or other degenerative processes. The binding of oATP with the receptors localized on many cells and also on sensory nerve terminals could competitively block the binding of extracellular ATP to the same structures, so limiting ATP-related cytotoxicity and inducing pain relief. Our results indicate also that oATP treatment in inflamed tissues limits further production of ATP by inflammatory or other cells possibly through a block of their activation.

Figure 3: Effect of oATP intraplantar injection on ATP levels of inflamed or noninflamed paws.

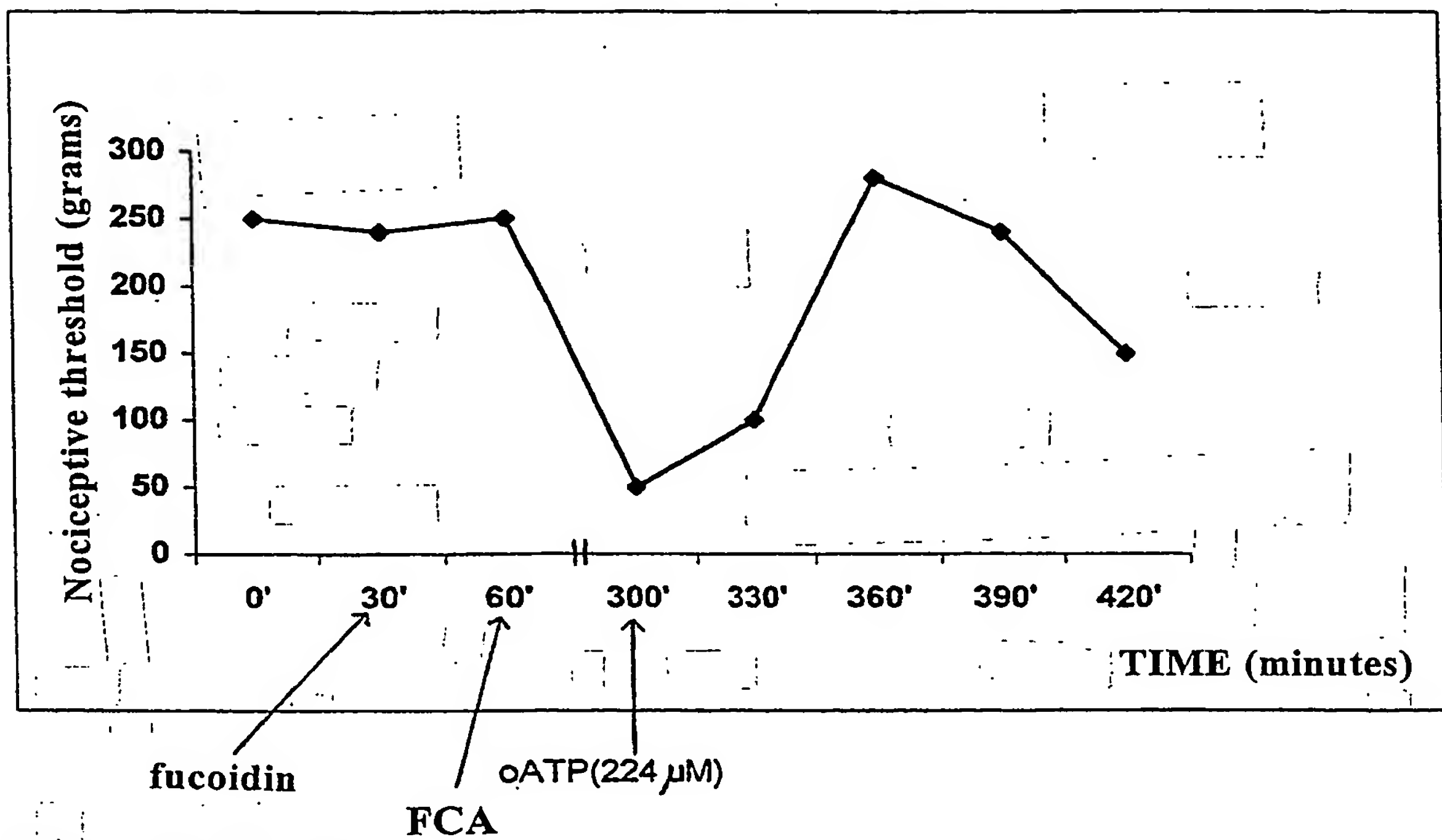
ATP content, at 6 and 12 h following intraplantar oATP (35 μ M) injection in rat paws: inflamed (by 24 FCA administration) (filled bars), inflamed-oATP treated (hatched bars), noninflamed (open bars), noninflamed-oATP-treated (horizontal line bars). * $p < 0.005$ compared with inflamed untreated paws, Wilcoxon test. Data are expressed as means \pm S.E.M. of 7 experiments.



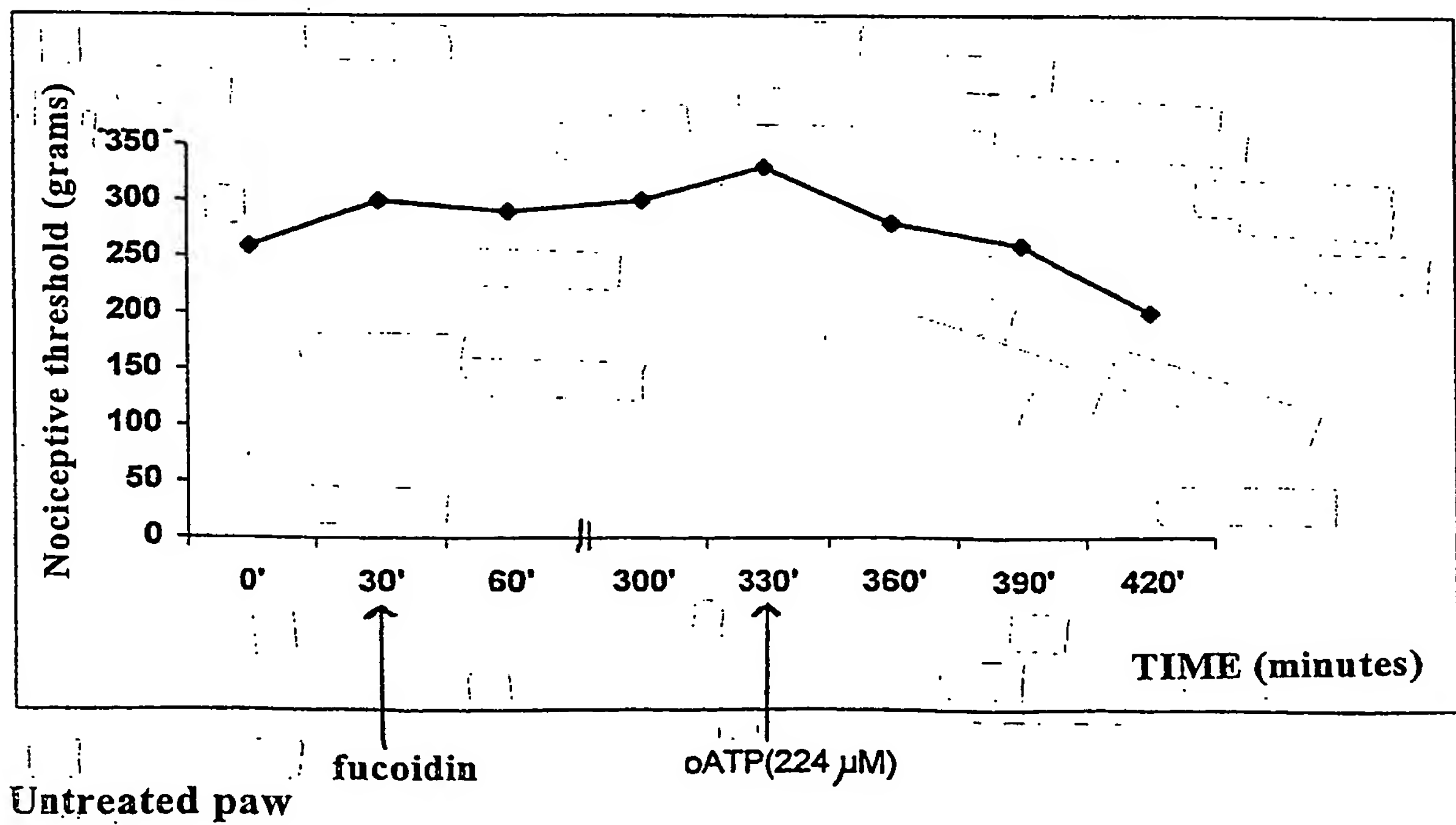
CLAIMS

1. The compound adenosine-5'-triphosphate-2',3'-dialdehyde for use as a medicament.
- 5 2. The compound of claim 1 for use in the treatment of inflammation and pain.
3. Pharmaceutical compositions containing adenosine-5'-triphosphate-2',3'-dialdehyde as active ingredient.

1/3

Figure 1

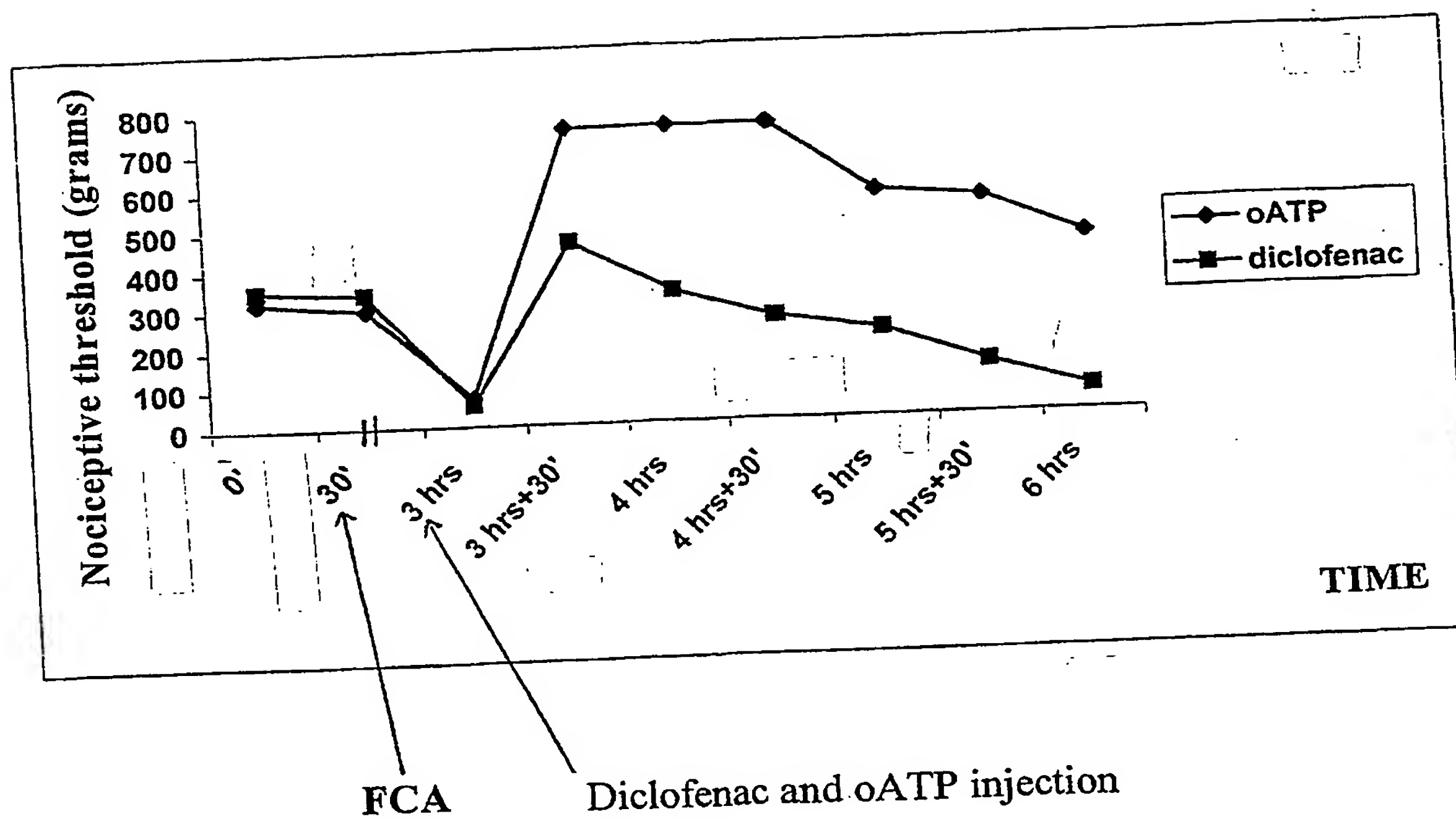
FCA - treated paw



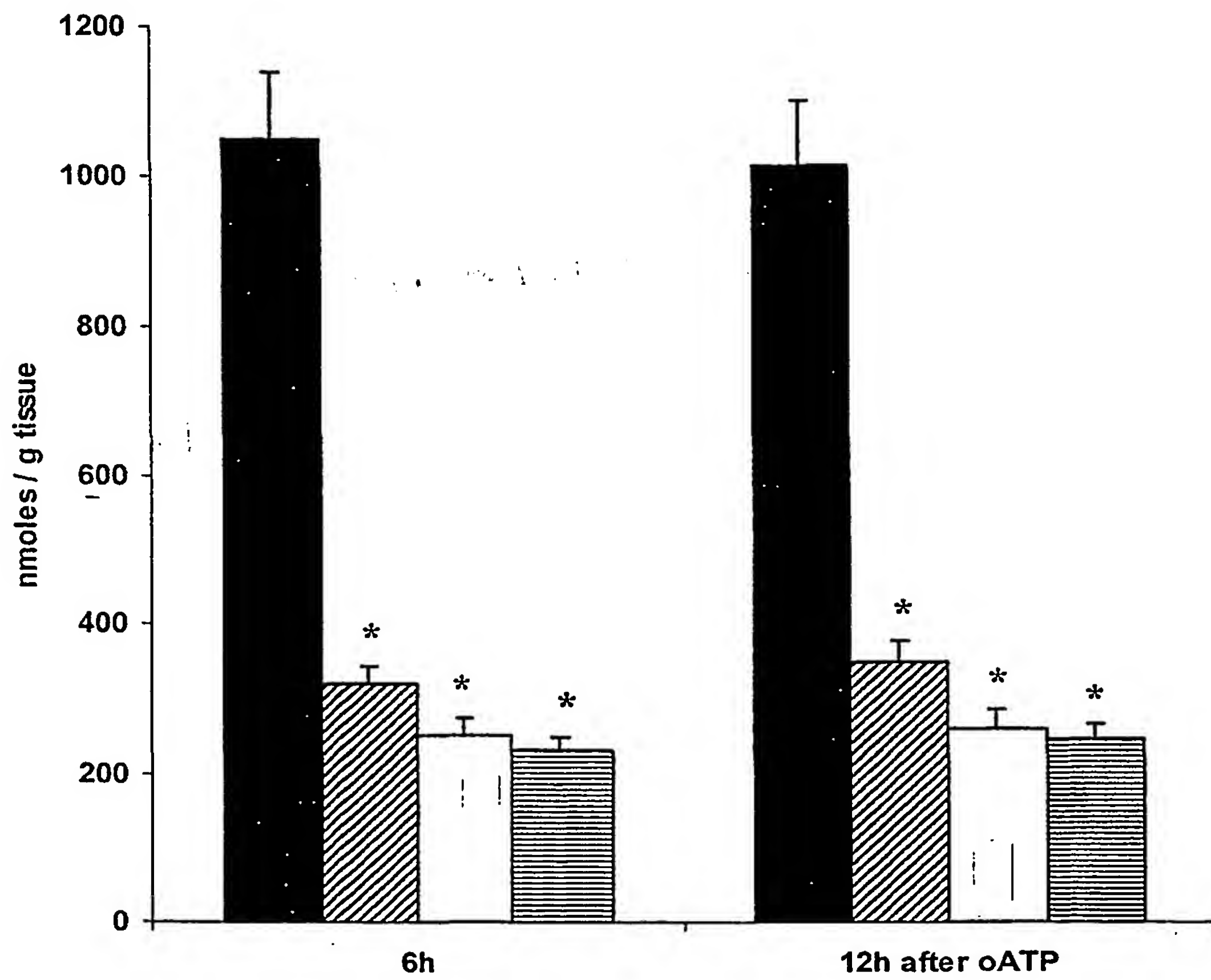
Untreated paw

2/3

Figure 2



3/3

Figure 3

THIS PAGE BLANK (USPTO)

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
14 February 2002 (14.02.2002)

PCT

(10) International Publication Number
WO 02/11737 A3

(51) International Patent Classification⁷: A61K 31/7076,
A61P 29/00

(21) International Application Number: PCT/EP01/08643

(22) International Filing Date: 26 July 2001 (26.07.2001)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
MI2000A001827 4 August 2000 (04.08.2000) IT

(71) Applicant (for all designated States except US): UNIVER-
SITA' DEGLI STUDI DI MILANO [IT/IT]; Via Festa del
Perdono, 7, I-20122 Milano (IT).

(72) Inventor; and

(75) Inventor/Applicant (for US only): FERRERO, Maria,
Elena [IT/IT]; Via Festa del Perdono, 7, I-20122 Milano
(IT).

(74) Agents: MINOJA, Fabrizio et al.; Bianchetti Bracco Mi-
noja S.r.l., Via Rossini, 8, I-20122 Milano (IT).

(81) Designated States (national): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,

CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK,
SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA,
ZW.

(84) Designated States (regional): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian
patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European
patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE,
IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF,
CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD,
TG).

Published:

- with international search report
- before the expiration of the time limit for amending the
claims and to be republished in the event of receipt of
amendments

(88) Date of publication of the international search report:
2 May 2002

For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.

(54) Title: ANTI-INFLAMMATORY MEDICAMENT

(57) Abstract: The use of adenosine-5'-triphosphate-2',3'-dialdehyde (oATP) as a medicament useful for the treatment of inflam-
matory conditions is disclosed.



WO 02/11737 A3

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 01/08643

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K31/7076 A61P29/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

BIOSIS, MEDLINE, CHEM ABS Data, EPO-Internal, WPI Data, PAJ, EMBASE, SCISEARCH

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
------------	--	-----------------------

X	<p>DI VIRGILIO FRANCESCO ET AL: "Purinergic P2X7 receptor: A pivotal role in inflammation and immunomodulation." DRUG DEVELOPMENT RESEARCH, vol. 45, no. 3-4, November 1998 (1998-11), pages 207-213, XP001056870 ISSN: 0272-4391 abstract page 210, left-hand column, paragraph 2 -page 211, right-hand column, paragraph 2</p> <p style="text-align: center;">--- -/--</p>	1-3
---	--	-----

☒ Further documents are listed in the continuation of box C.

☐ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *G* document member of the same patent family

Date of the actual completion of the international search

22 February 2002

Date of mailing of the international search report

12/03/2002

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Escolar Blasco, P

INTERNATIONAL SEARCH REPORT

Int. onal Application No
PCT/EP 01/08643

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category ~	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>SCHULZE-LOHOFF ECKHARD ET AL: "Extracellular ATP causes apoptosis and necrosis of cultured mesangial cells via P2Z/P2X7 receptors." AMERICAN JOURNAL OF PHYSIOLOGY, vol. 275, no. 6 PART 2, December 1998 (1998-12), pages F962-F971, XP002191118 ISSN: 0002-9513 abstract page F970, left-hand column, paragraph 4 ---</p>	1-3
X	<p>HU YUN ET AL: "Purinergic receptor modulation of lipopolysaccharide signaling and inducible nitric-oxide synthase expression in RAW 264.7 macrophages." JOURNAL OF BIOLOGICAL CHEMISTRY, vol. 273, no. 42, 16 October 1998 (1998-10-16), pages 27170-27175, XP002191119 ISSN: 0021-9258 abstract See Discussion ---</p>	1-3
X	<p>LIU JUDY S H ET AL: "Modulation of interleukin-1beta and tumor necrosis factor alpha signaling by P2 purinergic receptors in human fetal astrocytes." JOURNAL OF NEUROSCIENCE, vol. 20, no. 14, 15 July 2000 (2000-07-15), pages 5292-5299, XP002191120 ISSN: 0270-6474 abstract page 5298, left-hand column, paragraph 3 ---</p>	1-3
X	<p>MUTINI C ET AL: "Mouse dendritic cells express the P2X7 purinergic receptor: characterization and possible participation in antigen presentation." JOURNAL OF IMMUNOLOGY, (1999 AUG 15) 163 (4) 1958-65. , XP002191121 abstract page 1964, right-hand column, paragraph 3 -page 1965, left-hand column, paragraph 2; figure 7 --- -/--</p>	1-3

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 01/08643

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	SOLINI ANNA ET AL: "Human primary fibroblasts in vitro express a purinergic P2X7 receptor coupled to ion fluxes, microvesicle formation and IL-6 release." JOURNAL OF CELL SCIENCE, vol. 112, no. 3, February 1999 (1999-02), pages 297-305, XP002191122 ISSN: 0021-9533 abstract page 304, right-hand column, paragraph 2	1-3
X	SIKORA A ET AL: "Cutting edge: purinergic signaling regulates radical-mediated bacterial killing mechanisms in macrophages through a P2X7-independent mechanism." JOURNAL OF IMMUNOLOGY, (1999 JUL 15) 163 (2) 558-61., XP002191123 abstract page 560, right-hand column, paragraph 3 -page 561, left-hand column, paragraph 1; figure 4	1-3
X	PIZARRO J M ET AL: "EFFECT OF NUCLEOTIDE ANALOGUES ON ROTAVIRUS TRANSCRIPTION AND REPLICATION" VIROLOGY, vol. 184, no. 2, 1991, pages 768-772, XP001061622 ISSN: 0042-6822 abstract page 772, left-hand column, line 6 - line 10; table 1 page 769, left-hand column, line 5 - line 7	1,3